REMARKS

Claims 1, 152-170, and 172-187 are pending in this application. Claims 179-187 have been withdrawn from consideration by the Examiner as being drawn to non-elected inventions. The Office has also withdrawn claim 165 from consideration *sua sponte*, as well as certain subject matter of claims 1, 152-164, 166-170, and 172-178 without issuing a second restriction requirement (see Section IV of this response). Claim 177 has been amended to replace the term "or" with the term "and". No new matter has been added. After entry of the amendment, claims 1, 152-170, and 172-187 will remain pending in this application.

I. Information Disclosure Statement

Applicants have submitted an information disclosure statement herewith for the Examiner's consideration.

II. The Claims Are Enabled

Claims 1, 152-164, 166-170, and 172-176 are rejected as failing to comply with the enablement requirement with regard to certain compounds of claim 1 and with regard to the hydrates and solvates of the compounds of claim 1. As will be recognized, the enablement requirement of §112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation). In this respect, the following statement from *In re Marzocchi*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971), is noteworthy:

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained

> therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling.
>
> ... it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

Thus, any assertion by the Patent Office that an enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974). Applicants respectfully assert that the Office has not carried its burden to provide evidence or reasoning showing a sufficient reason to doubt the enablement of the claimed invention.

A. The Claimed Compounds Are Enabled

As mentioned above, the proper standard for an enablement inquiry rests on whether one skilled in the art would be able to make and use the invention without undue experimentation. *In re Wands*, 8 U.S.P.Q.2d at 1404. Factors for consideration in determining whether undue experimentation is necessary to make and use the invention include: 1) the quantity of experimentation necessary; 2) the amount of direction or guidance presented; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims.

The Office first acknowledges that the specification is enabling for compounds of claim 1 wherein W and Y are each an unsubstituted straight or branched C_{1-5} alkylene group, X is -O- or -S-, R_1 is H or C_{1-4} alkyl, and R_2 is H or C_{1-8} alkyl, but denies that the remaining subject matter of claim 1 is enabled. The Office states that the nature of the invention is compounds of Formula

(I), wherein X is -O-, -S-, -S(O)-, or -$S(O)_2$-, which are "are claimed to be useful for the treatment of a metabolic-related disorder" (Office Action, page 5). The level of skill in the art is acknowledged to be high (Office Action, page 6). As to the state of the prior art, the Office notes that no other compounds of Formula (I) are known to be pharmaceutically active (Office Action, page 6). As to the amount of guidance presented and the working examples, the Office alleges that the specification discloses only EC_{50} activity for compounds 48 and 63 (Office Action, page 7). The Office proceeds to allege that "most of the compounds claimed in the instant application [did] not exist at the time of the original filing, render[ing]the prior art unpredictable for making or using the products for pharmaceutical application as claimed on such a ground scale" (Office Action, page 7, *sic*). The Office then states that the existence of certain obstacles – such as the alleged necessity of *in vitro* and *in vivo* testing – would "prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face" (Office Action, page 7). Hence, the Office concludes it would require undue experimentation to determine "which product the process of using was describing" (Office Action, page 8).

Applicants respectfully assert that the Office has failed to provide sufficient reasoning or evidence showing a sufficient reason to doubt the enablement of the claimed invention. First, with regard to the compound claims, the Federal Circuit has established that *in vitro* tests showing a biological activity are sufficient to establish a practical utility for a genus of compounds, where there is a reasonable correlation between the disclosed *in vitro* activity and *in vivo* activity. *Cross v. Iizuka*, 224 U.S.Q.D. 739, 747-48 (Fed. Cir. 1985) (stating that "[w]e perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, in vitro testing, may establish a practical utility for the compound in question"). Further, the *Cross* court found that IC_{50} data for two related prior art compounds provided "sufficient credible evidence that one skilled in the art, without the exercise of inventive skill or undue experimentation, could determine IC_{50} dosage level for the [claimed] derivative", without explicit disclosure of those IC_{50} levels for the genus of compounds. *Cross*, 224 U.S.Q.D. at 748 (finding that the *Cross* case dealt with a "pharmacological activity or practical utility, i.e., not a therapeutic activity").

Similarly, the specification of the present application provides a method of assaying activity at the RUP25 receptor and provides EC_{50} data for the two examples (compounds 48 and 63) (specification, page 88, line 17 through page 89, line 4, describing a method of assaying activity using a 96-well plate). Just as in *Cross*, one of ordinary skill should be able to assay the compounds of claim 1 to determine their activity at the RUP25 receptor without undue experimentation by reference to the assay and the data for compounds 48 and 63. **Applicants further direct the Examiner's attention to the specification at page 69, lines 3-4, stating that the "majority of the compounds of the examples showed activities of at least about 60 μM".** The Examples in Table A, in turn, have differing values for each of the substituents, including X and W (specification, page 45-53). Hence, Applicants respectfully assert that the specification provides sufficient evidence demonstrating that compounds of Formula (I) bind to and agonize the RUP25 receptor.

Further, as in *Cross*, there is a reasonable correlation between the RUP25 receptor and the treatment of metabolic-related disorders. Nicotinic acid (niacin) was known to have efficacy in treating metabolic-related disorders prior to filing, as demonstrated by Guyton, "Effect of Niacin on Atherosclerotic Cardiovascular Disease", *Am. J. Cardiol.* 82(12A):17U-23U (1998) (hereinafter "Guyton", enclosed for the Examiner's convenience). Guyton summarizes six major clinical trials, some with niacin alone and some with niacin in combination with other agents, showing the efficacy in decreasing LDL chlolesterol and triglycerides, reducing long-term mortality rates from atherosclerotic events, reducing recurrent nonfatal myocardial infarction, raising HDL levels, and decreasing progression of coronary atherosclerosis. Further, nicotinic acid was known to reduce the level of free-fatty acids (see Tunaru, et al., "PUMA-G and HM74 are receptors for nicotinic acid and mediate its anti-lipolytic effect", *Nature Medicine*, 9(3):352-355 (March 2003), hereinafter "Tunaru", enclosed for the Examiner's convenience). Hence, Guyton and Tunaru demonstrate that there was ample evidence of the efficacy of nicotinic acid for treatment of metabolic-related disorders.

Further, nicotinic acid was known prior to filing to bind to a particular receptor – RUP25 – also known as the HM74A receptor or the GPR109A receptor (see GeneBank Accession No.

NP_808219 for the polypeptide referenced at page 3, lines 6-9 of the specification, in the definition of RUP25; see also, Wise, et al. "Molecular Identification of the High and Low Affinity Receptors for Nicotinic Acid", *J. Biolog. Chem.*, 278(11):9869-9874 (2003), enclosed for the Examiner's convenience). The murine homologue of HM74A – RUP25 – is known as PUMA-G. Studies conducted before the date of filing showed PUMA-G mediates the main metabolic effects of nicotinic acid, including lowering free-fatty acid and triglyceride levels (see Tunaru, pages 352-355). Studies also showed that nicotinic acid inhibited intracellular cyclic adenosine monophosphate (cAMP) in cells transfected with PUMA-G (see Tunaru, page 352). cAMP is tied to lipolysis involved in dyslipidemia and the down-regulation of the secretion of adiponectin involved in atherosclerosis (see Tunaru, page 352; Delporte, et al., "Pre- and post-translational negative effect of β-adrenoceptor agonists on adiponectin secretion: *in vivo* and *in vitro* studies", *Biochem. J.* 367:677-685 (2002); Okamoto, "Adiponectin reduces atherosclerosis in apolipoprotein e-deficient mice", *Circulation*, 106:2767-2770 (2002); and Matsuda, "Role of adiponectin in preventing vascular stenosis: the missing link of adipo-vascular axis", *J. Biol. Chem.*, 277(40):37487-37491 (2002) (each of which is enclosed for the Examiner's convenience), for support for (a) that nicotinic acid inhibits cAMP accumulation; (b) that cAMP is a down-regulator of adiponectin secretion; and (c) that elevated levels of adiponectin significantly suppress the formation of atherosclerotic lesions in mice, while reduced levels result in augmented intimal proliferation in the vascular walls of adiponectin-null mice). Hence, there is ample pre-filing evidence tying the RUP25 receptor to the efficacy of nicotinic acid in treating metabolic-related disorders such as those of the claimed methods.

Further, nicotinic acid was known to function as an agonist at the RUP25 receptor (see Wise, page 9872). Hence, other agonists of the RUP25 receptor should have efficacy in treating the same disorders treatable by nicotinic acid. As discussed previously, Applicants' specification contains data showing the ability of certain compounds of Formula (I) to bind to and agonize the RUP25 receptor, as does nicotinic acid itself.

In light of the state of the art at the time of filing as summarized above, (1) nicotinic acid (niacin) was known at the time of filing to have activity in treating the particular metabolic-

related disorders recited by the claims; (2) the murine variant of the known RUP25 receptor was shown to mediate the metabolic effects of nicotinic acid; (3) nicotinic acid was known to bind to and agonize the RUP25 receptor; and (4) Applicants' specification demonstrates the ability of compounds of Formula (I) to bind to and agonize the RUP25 receptor. As a result, one of skill in the art would recognize that an agonist of the RUP25 receptor, such as the compounds claimed in the present application, would be expected to have efficacy in treating the same disorders that are treatable with nicotinic acid. Accordingly, in light of the working examples described above, the guidance provided by the specification, and the state of the art regarding the RUP25 receptor and nicotinic acid, Applicants assert one of skill in the art could have practiced the claimed methods at the time the present application was filed without undue experimentation and with a reasonable expectation of success. The Office has failed to point to any evidence to doubt the objective truth of the statements contained by the specification as required by in *In re Marzocchi.* Applicants, therefore, request that the claim rejections be withdrawn.

B. The Solvates and Hydrates of the Claimed Compounds Are Enabled

Claims 1, 152-164, 166-170, and 172-178 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement with regard to the solvates and hydrates of the claimed compounds. The Office alleges that "the specification does not reasonably provide enablement for forming crystalline [solvates and hydrates] of each of the compound list in the claims", "due to the high level of unpredictability associated with crystalline of the compounds" (Office Action, page 9). The Office cites Vippagunta, Brittain, and Grant, "Crystalline Solids", 48 (2001), 3-26, in support of its contention (hereinafter "Vippagunta").

Applicants respectfully assert that the Office has not carried its burden to provide evidence or reasoning showing a sufficient reason to doubt that one of skill in the art could make the hydrates and solvates of the claimed compounds without undue experimentation. As will be appreciated, the test for whether experimentation would be undue is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine. *Wands*, 8

U.S.P.Q.2d at 1404. In *Wands*, the Office had rejected the appealed claims, directed to methods for assaying HBsAg using high-affinity IgM monoclonal antibodies, as lacking enablement. *Id.* at 1402. The Office alleged that the production of high-affinity IgM anti-HBsAg antibodies was unpredictable and unreliable and, therefore, would require undue experimentation. *Id.* The Federal Circuit disagreed, finding that undue experimentation would not be required. *Id.* at 1406. Even though screening for hybridomas involved several, labor-intensive steps (see the steps in Table 1), the court found that this amount of effort was not excessive or undue, as the methods needed to practice the invention were well-known and the level of skill in the art was high. *Id.* The court noted that a finding of undue experimentation would not be required even if the success rate for producing the antibodies was only 2.8% as suggested by the Office (as contrasted with the 44% success rate advanced by the applicant). *Id.*

In stark contrast with the antibody-making procedures at issue in *Wands*, the preparation of hydrates and solvates of a particular organic molecule is a substantially easier and overwhelmingly simpler process, which requires significantly fewer steps and much less time than the preparation of a monoclonal antibody. Table 1 provides a step-by-step comparison of some of the major steps involved in the production of a monoclonal antibody (as disclosed in *Wands*) and the one step involved in making a hydrate or solvate. To make hydrates and solvates, samples of the organic compound are exposed to water or various different solvents.[1] Once the hydrates and solvates are formed, they can be readily analyzed by routine methods

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[1] For example, Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids", in Polymorphism in Pharmaceutical Solids, ed. Harry G. Brittain, vol. 95, chapter 5, Marcel Dekker, Inc., New York 1999, pages 183-226 (hereinafter "Guillory") at pages 202-205 and pages 205-208 describe the routine preparation of hydrates and solvates of compounds, respectively, as illustrated in the excerpts below:

> Simply exposing an anhydrous powder to high relative humidity can often lead to formation of a hydrate.

Guillory, page 204.

> Often, when solvents are employed in the purification of new drug substances by recrystallization, it is observed that the isolated crystals include solvent molecules...

Guillory, page 205.

(page 18, right column, of Vippagunta) or other routine techniques to detect and quantify the presence of hydrate or solvate molecules in the sample. Exposure of the organic compounds to water and various solvents is conducted through simple and routine methods such as letting the samples sit open to air for set amounts of time, as well as slurrying and/or crystallizing the samples from water or solvent. In fact, it is difficult to conceive of a scientific method that is simpler to perform than placing a powder on a dish and letting it sit out on a humid day. Other typical procedures for making and identifying hydrates and solvates are described in Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids", in Polymorphism in Pharmaceutical Solids, ed. Harry G. Brittain, vol. 95, chapter 5, Marcel Dekker, Inc., New York 1999, pages 183-226 (hereinafter "Guillory") (enclosed). Hence, screening for hydrates and solvates merely uses methods that are very well known in the art and considered quite simple.[2] As is clearly shown in Table 1 and summarized above, the production of a monoclonal antibody is much more complex and time-consuming than the production of a hydrate or solvate, yet the *Wands* court concluded that the production of a monoclonal antibody was not excessive and undue. Hence, it is clearly inconsistent to allege that the production of hydrates and solvates would require undue experimentation, while the production of monoclonal antibodies would not require undue experimentation.

The Office attempts to base its enablement rejection on unpredictability of solvate formation and (2) lack of working examples. Unpredictability was a major reason for the Office's rejection of the claims in *Wands*, yet the rejection was reversed by the Federal Circuit because, in part, all the methods needed to practice the invention were well-known and the level in the art was high. Accordingly, any unpredictability associated with hydrate or solvate formation that might exist is clearly outweighed by the fact that preparing and screening for hydrates and solvates is routine and employs well-known methods. Further, the Office's own reference suggests that crystalline forms are quite common, stating that "[m]ost organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms"

[2] In fact, there are numerous companies that routinely provide this screening service (usually combined with polymorph screens) and advertise how quickly and efficiently they can identify hydrates and solvates. Example companies offering these services include Wilmington PharmaTech (Wilmington, DE) and Avantium Technologies (Amsterdam).

(Vippagunta, page 4). This statement appears to contradict the Office's supposition that one of skill in the art would doubt the ability of compounds of the present application to form hydrates and solvates. With respect to lack of working examples, the courts have held that there is no requirement for a "working" example if the disclosure is such that one skilled in the art can practice the claimed invention. *In re Borkowski,* 164 U.S.P.Q. 642 (C.C.P.A. 1970); *Ex parte Nardi*, 229 U.S.P.Q. 79 (Pat. Off. Bd. App. 1986). Given that one skilled in the art could make and identify various hydrates and solvates of a particular organic molecule using the routine screening methods discussed above, no working example is necessary to enable the invention. Because preparation of hydrates and solvates merely involves the use of well known methods and would not require excessive effort, Applicants respectfully assert that the hydrates and solvates can be made without undue experimentation and request that the claim rejections be reconsidered and withdrawn.

Table 1

Step	Monoclonal Antibody	Hydrate or Solvate
1	immunize animal	expose the compound to water or solvent
2	remove the spleen from the immunized animal	
3	separate the lymphocytes from the other spleen cells	
4	mix the lymphocytes with myeloma cells	
5	treat the mixture to cause fusion between the lymphocytes and the myeloma cells to make hybridomas that hopefully secrete the desired antibody	
6	separate the hybridoma cells from the unfused lymphocytes and myeloma cells by culturing in a medium in which only hybridoma cells survive	

Step	Monoclonal Antibody	Hydrate or Solvate
7	culture single hybridoma cells (often 100 of different cells) in separate chambers	
8	assay the antibody secreted from each hybridoma culture to determine if it binds to the antigen	

III. The Claims Have Written Description

Claims 1, 152-164, 166-170, and 172-178 are rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. In particular, the Office alleges that the specification does not describe even a single example of a crystal form of a solvate or hydrate (Office Action, page 10). Hence, the Office concludes that the specification does not "reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" (Office Action, page 10).

Applicants respectfully assert that the specification contains sufficient written description to convince one of skill in the art that Applicants had possession of the hydrates and solvates of the claimed compounds. As will be appreciated, examples and a reduction to practice are not required in order for the specification to put one skilled in the art in possession of the claimed invention, particularly when the art at the time of filing would convince one of skill in the art that the inventor possessed the invention. *See Falkner v. Inglis*, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006) (holding that a reduction to practice of a pox virus vaccine was unnecessary for the claimed invention to satisfy the written description requirement, where the art described essential genes for poxvirus). As stated by the Federal Circuit:

> A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation.

Id.

Hence, the absence of examples of hydrates and solvates of the claimed compounds is not sufficient to demonstrate that the invention lacks written description. Instead, the focus should be on whether the specification and the knowledge in the art at the time of filing would convince one of skill in the art that Applicants were in possession of the hydrates and solvates of the claimed compounds. The specification describes the synthesis and purification of various examples of the compounds of Formula (I). Further, the art, as evidenced by Guillory, is replete with methods for preparing and characterizing solvates and hydrates of compounds (see Section I of this response). Additionally, the art teaches that solvates and hydrates can routinely form during purification steps and exposure to solvent or water (see Section I of this response). Given the routine methods of forming solvates and hydrates in the art, one of skill in the art would be convinced that Applicants possessed the hydrates and solvates of the Formula (I) compounds.[3] Accordingly, Applicants respectfully assert that the solvates and hydrates of the claimed compounds meet the written description requirement and request that the claim rejections be withdrawn.

IV. The Claimed Compounds Are Patentably Distinct

Claims 1, 152-164, 166-170, and 172-178 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-2, 5-14, 20-28, and 30 of U.S. Patent Appl. 10/530,902 (hereinafter "the '902 application"). The Office recognizes that the claims of the present application contain heteroatoms in the linking group at the 5-position (e.g., X), while those of the claims of the '902 application have a bond or alkylene linker (e.g., aryl-C_{1-4}-alkylene or heteroaryl-C_{1-4}-alkylene). Nonetheless, the Office alleges that compounds are so structurally similar that one of skill in the art "knowing properties of one member of series would in general know what to expect in adjacent members" (Office Action, page 12). The Office insists this is particularly true because the claimed compounds "have the same utility as a

[3] Indeed, U.S. patents are replete with claims reciting the pharmaceutically acceptable salts of claimed compounds.

pharmaceutical compound or composition" as the claimed compounds of the '902 application (Office Action, page 12).

Applicants respectfully assert that the compounds of claims 1, 152-164, 166-170, and 172-178 are patentably distinct from those of claims 1-2, 5-14, 20-28, and 30 of the '902 application. By referring to the alleged structural similarity of the compounds of the two applications, the Office is presumably referring to the principals laid out in *In re Dillon*, U.S.P.Q.2d 1897, 1901 (Fed. Cir. 1990). Under *Dillon*, a *prima facie* case of obviousness can be established when the claimed compound and prior art compounds are so structurally similar so as to provide a motivation to make the claimed compound in the expectation that it will have the same properties as the prior art compound. *Id.* at 1901. In *Dillon*, the court affirmed that the tetra-orthoester of the claimed composition was so structurally similar to the tri-orthoester of the prior art reference that there would have been a motivation to modify tri-orthoester prior art composition to obtain the claimed composition. *Id.*

The Federal Circuit, however, has refused to overextend this doctrine to compounds which are not homologs of each other. For example, in *Jones*, the Federal Circuit did not consider a claimed amine salt *prima facie* obvious over a prior art amine salt, because the two salts had notable structural differences. *In re Jones*, 21 U.S.P.Q.2d 1941, 1942 (Fed. Cir. 1992). The court pointed out the prior art salt lacked an ether linkage and was a secondary amine, while the claimed amine salt had an ether linkage and was a primary amine. *Id.* Accordingly, the court refused to consider the claimed salt and the prior art salts "'so closely related in structure' as to render the former *prima facie* obvious in view of the latter." *Id.* The court made this finding despite the fact that the claimed salt fell within the genus disclosed in the prior art patent and had the same herbicidal activity as the compounds in the prior art patent. *Id.* at 1942.

Just as the compounds in *Jones* differed from the compound in the art by having an ether linkage, the claimed compounds of the present application have a heteroatom-containing linker while those of the claims of the '902 application have a simple alkyl or haloalkyl group, an alkylene linker, or have no alkylene linkage at all. Hence, just as in *Jones*, the claimed compounds of the present application should not be considered to be obvious variants of the

claimed compounds of the '902 application. Further, the compound claims of the present application do not fall within – or, indeed, overlap generically with – the claims of the '902 application, unlike the claimed compounds in the *Jones* application which fell within the genus of the prior art patent. Hence, this case presents a stronger case of non-obviousness than *Jones*. Accordingly, for all of these reasons, Applicants respectfully assert that the claimed compounds are not obvious variants of the claimed compounds of the '902 application and request that the claim rejections be withdrawn.

V. The Claims Do Not Contain Non-Elected Subject Matter

Claim 166 is objected to as containing "non-elected" subject matter (Office Action, page 12). Applicants respectfully assert that claim 166 does not contain "non-elected" matter, as the Office is improperly introducing a further limitation in this Office Action which goes beyond the original Restriction Requirement. On June 14, 2007, the Office mailed a Restriction Requirement, setting forth a 13-way restriction requirement and an election of species requirement. In response, Applicants elected with traverse Group X and a species for initial search purposes (compound 63). Group X was set forth in the Restriction Requirement as follows:

> Group X: Claims 1, 3, 151-167, and 170-178, drawn to a compound of formula (I) wherein m is 1, n is 1, Z is H or halogen, or a composition comprising said compound. This group may be subject to further restriction if elected.

(Restriction Requirement at page 5).

In this Office Action, the Office states the "elected subject matter and the examined subject matter" as follows:

> Compounds of Formula I...wherein X is -O-, -S-, -S(O)-, or -$S(O)_2$-; and the remaining substitutents as defined in claim 1, or pharmaceutically acceptable salt, solvate, or hydrate or a pharmaceutical composition comprising the said compound in claim 1.

(Office Action, page 3). This version of the "elected subject matter and the examined subject matter" directly conflicts with the original Restriction Requirement, as elected Group X did not

recite that X is -O-, -S-, -S(O)-, or -$S(O)_2$. Hence, claim 166, reciting that X is -CH(OH)-, -C(NH)-, O-, -S-, -S(O)-, or -$S(O)_2$- cannot be considered to contain "non-elected" subject matter, as Group X included all of the recited values for X. Indeed, it is hard to fathom how claim 166 could contain "non-elected" subject matter, as the Office never presented the subject matter reciting that X is -O-, -S-, -S(O)-, or -$S(O)_2$- for election in the first place. Accordingly, Applicants respectfully request that the objection to claim 166 be withdrawn.

Further, Applicants respectfully request reconsideration of the Office's withdrawal of this subject matter from consideration, as this withdrawal was made improperly and arbitrarily without reference to the proper substantive standards. First, this withdrawal is clearly procedurally improper. The Office has failed to issue a second restriction requirement and, instead, has preemptively withdrawn subject matter from examination. This is clearly outside the bounds of proper restriction practice, which requires that "the examiner must (1) list the different groups of claims and (2) explain why each group lacks unity with each other group (i.e., why there is no single general inventive concept) specifically describing the unique special technical feature in each group." M.P.E.P. § 1893.03(d). The Office has clearly failed to make any kind of listing (particularly of compounds with differing values for X), much less state reasons for why the groups lack unity of invention with each other. Indeed, even assuming this withdrawal of subject matter was procedurally proper, the Office uses incorrect legal standards, stating that the "withdrawn compounds...are **patentably distinct** from the elected subject matter" (Office Action, page 3, emphasis added). As this application is a National Stage application, the proper legal standard for restriction is unity of invention, not patentable distinctness.

Further, while the Office also made an election of species requirement, this withdrawal of "non-elected" subject matter is completely outside the procedures for examination where a provisional election of species has been required in an application. M.P.E.P. § 803.02 states that the Office shall initially search the elected species and any other species considered to be clearly unpatentable over the elected species. If prior art is found **to anticipate or render obvious** the elected species, then the Office should reject the Markush-type claim and the claims to the

elected species and withdraw the nonelected species from further consideration. M.P.E.P. § 803.02. As the Office has failed to find any prior art which anticipates or renders obvious the elected species, this withdrawal of subject matter from examination is improper.[4] For all of these reasons, Applicants respectfully request that the Office reconsider its withdrawal of the "non-elected" subject matter.

In addition to these procedural and substantive difficulties, the withdrawn subject matter appears to be both broader and narrower than Group X. It narrows Group X by reciting certain values of X, but broadens Z by stating the remaining substituents, other than X, are "as defined in claim 1". Claim 1 recites that Z is H, halogen, phenyl, or heteroaryl (wherein phenyl and heteroaryl are optionally substituted), while Group X recited that Z is H or halogen. Hence, in the event that the Office does not reconsider the withdrawal of the "non-elected" subject matter, Applicants respectfully request clarification of scope of the withdrawn subject matter so that their rights under 35 U.S.C. § 121 are preserved.

VI. Remaining Claim Objection

Claim 178 is objected to as being an inappropriate Markush-type claim for the presence of the term "or". Claim 178 has been amended to replace the term "or" with the term "and". Accordingly, Applicants respectfully assert that this amendment renders the objection moot and request that the claim objection be withdrawn.

VII. Conclusion

Applicants respectfully assert that rejections and objections of record have been overcome by way of this response. Allowance of all claims is respectfully requested. The Examiner is urged to contact Applicant's undersigned representative at (302) 778-8411 if there are any questions regarding the claimed invention.

The Commissioner is hereby authorized to debit any fee due or credit any overpayment to Deposit Account No. 06-1050. Further, if not accompanied by an independent petition, this

[4] Applicants also remind the Office that M.P.E.P. § 803.02 provides that examination must be extended upon an Applicant overcoming a rejection which "anticipates or renders obvious the Markush-type claim".

paper constitutes a Petition for an Extension of Time for an amount of time sufficient to extend the deadline and authorizes the Commissioner to debit the petition fee and any other fees or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: August 28, 2008

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Enclosures: Information Disclosure Statement and 1449 Form
Copies of Guillory, Guyton, Tunaru, Wise, Delporte, Okamoto, and Matsuda references
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